Chapter 1 - Introduction

Exercise training has been shown to improve functional capacity and is recommended by several guideline documents as a useful therapy for chronic heart failure (CHF) patients (Gianuzzi et al., 2001; Krum et al., 2006; Selig et al., 2010). A review of the literature yields important information related to the effects of exercise training in CHF patients. However, improved survival in CHF patients is yet to be evidenced in spite of advances in drug therapy and exercise training. It has been speculated that the lack of evidence of improved survival could be due to poor implementation of current guidelines as well as sub-optimal exercise programming. Therefore, this body of work has been designed to address and explore some important issues in improving prognosis in heart failure patients and attempt to establish the optimal exercise protocol which should be individually tailored to patients. This work seeks to add to the evidence-base of safe and practical guidelines for the implementation of exercise training in heart failure (HF) patients. The studies presented in chapters three, four, five and seven are retrospective analysis of published studies. This thesis has been divided into several chapters and recommendations have been made to enhance future data analyses of this nature.

1.1 Chapter 1 – Introduction

This chapter emphasizes the conceptual frame work of the entire thesis, stating the research questions and aims of the analyses.

1.2 Chapter 2 – Literature reviews on pharmacological and non-pharmacological management of heart failure patients

The issues addressed by this work were based upon literature reviews that related to the pathology and epidemiology of heart failure, general therapy for heart failure patients, benefits and safety of exercise training in cardiac patients and factors affecting response to exercise training.

1.3 Chapter 3 – Beta-blockade Medication in Chronic Heart Failure Patients

Beta-blocker therapy is a component of the cornerstone of pharmacological management which has been widely used for medication of heart failure patients and exercise training is perhaps the non-pharmacological equivalent, it is important to understand the relationship between these therapies. Therefore, three comparisons were conducted in this analysis. First we compared studies between groups who did and did not take B-blocker medication during exercise training. Second we compared selective and non-selective B-blockers during exercise training. Third we compared those who exercise versus sedentary control in patients taking B-blocker.

Research questions and aims of the study

a. The primary aim was to establish if beta-blockers attenuated physical training adaptations in heart failure patients.

b. The secondary aim was to establish if selective or non-selective beta-blockers were more beneficial to those people with heart failure undertaking exercise training.

c. Finally, this work aimed to establish if quality of life was better in those people with heart failure who were or were not taking beta-blockers during exercise training.

1.4 Chapter 4 – Exercise Prescription for Chronic Heart Failure

The primary aim of this work was to establish if exercise intensity influenced effect sizes for change in peak VO2. We therefore compared high, vigorous, moderate, low intensity exercise training and sedentary controls in published studies of heart failure patients. Secondly, we wished to establish if exercise intensity or interval training produces better adherence and rates of serious events, mortality and hospitalization in heart failure patients.

Research questions and aims of the study

a. Will high intensity interval training have an impact on clinical outcomes in chronic heart failure patients? We aimed via systematic review to establish if high intensity interval training produces different effect size for change in peak VO_2 compared to vigorous, moderate and low intensity training and sedentary controls in heart failure patients.

b. Is high intensity really safe in HF patients? We analysed all clinical randomized controlled trials of exercise training in chronic heart failure patients.

c. Will high intensity interval training improve adherence to exercise training in HF patients? We wished to establish if exercise intensity or interval training produces better adherence.

d. Are rates of serious events, mortality and hospitalization more frequent with exercise intensity in heart failure patients?

e. What is the optimal exercise training protocol to be used for chronic heart failure?

1.5 Chapter 5 – Exercise Training Program Characteristics and Magnitude of Change in Functional Capacity of Heart Failure Patients

The aim of this work was to establish which, if any, exercise program characteristics had the greatest influence on effect sizes for change in peak VO_2. This study also examined if rates of serious events, mortality and hospitalization were more frequent with any particular exercise program characteristics in heart failure patients.

Research questions and aims of the study

a. Which exercise program characteristics, if any, produced the largest improvements in peak VO_2?

b. Are rates of serious events, mortality and hospitalization more frequent with any particular exercise program characteristics in heart failure patients?

1.6 Chapter 6 – Study Protocol for Chronic Heart Failure

In the light of the findings above we therefore designed a trial based upon what we interpret as a natural progression to extend the published literature and this will serve as a future direction trial in CHF patients.

1.7 Chapter 7 – Exercise Prescription for preserved ejection fraction (HFpEF)

This chapter presents a study on heart failure with preserved ejection faction (HFpEF) patients. The aim of this work was to establish if exercise training produces changes in peak VO_2 and related measures, quality of life, general health and diastolic function in heart failure patients with preserved ejection fraction.

Research questions and aims of the study

a. Will exercise training produced larger effect sizes for change in exercise capacity and diastolic function compared to sedentary controls in HFPEF patients?

b. Will exercise training produces better quality of life?

c. Are rates of serious events, mortality and hospitalization were more frequent with exercise training in HFpEF patients?

1.8 Chapter 8 – Study quality and reporting scale for exercise science in clinical population (developing TESTEX)

Based upon difficulties experienced when conducting study quality and reporting assessment for meta-analyses, a study quality and reporting assessment scale, specific to exercise training studies in people with chronic disease, was developed. This scale was designed for use by exercise specialists to assess the quality and study reporting of randomized, controlled trials of exercise training in clinical populations. Therefore, several published exercise training studies were evaluated using a new scale, namely TESTEX criteria.

Research questions and aims of the study

a. The aim was to develop a new study quality assessment tool to improve overall study design and reporting which, in turn will strengthen inferences and conclusions made from the data provided.

b. To establish the validity and reproducibility of the scale, a reliability study was conducted.

1.9 Chapter 9 – Conclusion

This work is novel in that a mortality benefit through high intensity exercise training has not been established previously. The results from high intensity interval training or moderate continuous training may provide an objective framework for designing a safe and more efficacious program based in heart failure patients.

Chapter 2 – Literature reviews on pharmacological and non-pharmacological management of heart failure patients.

2.1 Introduction

Chronic heart failure (CHF) is a type of heart failure (HF) which requires timely medical attention. It is a pathophysiological state with the epidemiology of a clinical syndrome relating to a range of cardiovascular and non-cardiovascular conditions. It is a condition that is more prevalent with age, affecting humoral, neuroendocrine, renal and musculoskeletal systems.

Heart Failure with reduced ejection fraction (HFrEF) is a complex clinical syndrome that results from structural or functional impairment of ventricular filling or ejection of blood. The signs and symptoms of heart failure (HF) are dyspnoea and fatigue, which limit exercise tolerance, and fluid retention. In some cases, patients have exercise intolerance but little evidence of fluid retention, whereas others complain primarily of oedema, dyspnoea, or fatigue. The term "heart failure" is preferred over "congestive heart failure" because some patients present no signs or symptoms of volume overload. There is no single diagnostic test for HF as it is largely a clinical diagnosis based on a careful history and physical examination (Yancy et al., 2013).

Additionally, heart failure with preserved ejection fraction (HFpEF) is the inability of the ventricles to accept the blood ejected from the atria with a blunted end-diastolic volume response, limiting stroke volume and cardiac output (Bhatia et al., 2006; Lam, Donal, Kraigher-Krainer, & Vasan, 2011). HFpEF prevalence is growing and results in substantial morbidity, mortality and healthcare costs than HFrEF. Nearly 50% of HF patients in the clinical practice setting are HFrEF, (Liao et al., 2006; Owan et al., 2006), however, the focus of w o r k is on HFrEF patients.

2.2 Heart Failure Pathology

Heart failure (HF) is recognized by signs and symptoms related to low cardiac output and congestion such as exercise intolerance, chronic fatigue, fluid retention and reduced left ventricular ejection fraction (LVEF). The long-term detrimental effects of neurohormonal activation in chronic heart failure patients result in decreased cardiac function, increased vasoconstriction and hence lead to exercise intolerance. Fluid overload in heart failure patients is due to abnormal neurohormonal mechanisms and elevated adrenergic tone in the myocardium, mediating progressive left ventricular dysfunction (LVD) and structural remodelling marked by dilation, hypertrophy, and declining LVEF (Arroll, Doughty, & Andersen, 2010; Braith & Edwards, 2003; Reyes, 2002). In contrast to the understanding that the leading cause of heart malfunction is related to a pump, there has been mounting evidence that the complex evidence of pathophysiology of CHF begins with an abnormality

of the heart but involves others adaptive changes in many body organs and systems including the inflammatory systems, renal, musculoskeletal systems, homeostatic and immune systems. These changes perhaps are indicators of the HF syndromes and its progression (M. F. Piepoli & Coats, 2013).

The sympathetic nerves and the renin-angiotensin-aldosterone system activate adverse haemodynamic consequences such as raised jugular venous pressure, crepitation sounds on chest auscultation, hepatomegaly and signs of peripheral oedema (Arroll et al., 2010; Klapholz, 2009). Nitric Oxide (NO) production is impaired due to reduced endothelial nitric oxide synthase (eNOS) expression or activity by asymmetric dimethyl arginine, NO scavenging by reactive oxygen species, and reduced availability of L-arginine and tetrathydropbiopterin (M. F. Piepoli, 2013). However, the clinical diagnosis of heart failure can be complex due to few clinical signs, absence of systemic congestion and absence of acute symptoms. Additionally, exercise intolerance and reduced quality of life are known as the primary chronic symptoms in HFpEF patients. HFpEF prevalence is higher in elderly and women and may be linked to hypertension, diabetes mellitus and atrial fibrillation (Lam et al., 2011).

2.3 Epidemiology of Heart Failure

Chronic Heart Failure (CHF) is an epidemic and a leading cause of mortality and morbidity worldwide (Mosterd & Hoes, 2007). Over 300,000 Australians have heart failure and another 30,000 new cases are

diagnosed, with 43,000 hospitalizations and 2,200 deaths, each year (Scott & Jackson, 2013). In the United States of America, chronic heart failure affects approximately 5 million individuals with heart failure and over 555,000 are newly diagnosed as CHF annually (Roger et al., 2012).

Though, in spite of sufficient epidemiology data in developed countries, there is insufficient information of CHF epidemiology data in other regions. In Malaysia, in a single centre-based study, data showed that the prevalence of HF among 1435 acute medical admissions to the Kuala Lumpur General Hospital was 6.7% during a 4-week study period (Chong, Rajaratnam, Hussein, & Lip, 2003). In Japan, around 1.0 million individuals have CHF and it is has been predicted that the number of Japanese outpatients with left ventricular (LV) dysfunction gradually increased from 979,000 in 2005 to 1.3 million by 2030. Meanwhile in China, more than 4 million individuals have HF and 500,000 new cases of CHF are diagnosed annually. Cardiovascular disease is also the leading cause of death in China (Sakata & Shimokawa, 2013). Geographic variations in access to diagnostic testing may explain lower prevalence for heart failure in developing countries such as China. Based on the ratio of population from two countries, China (1.2 billion) versus USA (350 million), only 4 million in China were diagnosed with heart failure compared to 5 million in USA. Moreover, the epidemiology of CHF has a strong association with certain demographic characteristics (Najafi, Dobson, Hobbs, & Jamrozik, 2008), for example CHF mortality increases with increasing geographical

remoteness. The Australian Institute of Health and Welfare (AIHW) reported that the 2003 mortality rate in CHF patients is between 20% and 50% higher in rural areas compared with major cities (Clark et al., 2005).

The National Health Service (NHS) reported CHF risk factors in Australian patients aged >55 between 1995 and 2004, it was estimated that 58% lived in the capital Sydney, while the remainder of the cases were evenly distributed between large urban centres and rural and remote regions (21%). CHF affects more males (54%) than females (46%) and most of the patients have symptomatic CHF associated with both left ventricular systolic dysfunction (LVSD) and diastolic dysfunction with 26% of patients living in rural and remote regions (Clark et al., 2005). The cost to the health care system for Chronic Heart Failure in Australia has been estimated at more than $1 billion per year (Krum et al., 2006). A review by Smart in 2011 (N. Smart, 2011) compared treatment costs to prevent mortality in one CHF patient; with the estimated cost (AUS$) per annum hospital-based exercise at AUS$ 60,000 which is comparable in cost to Beta-Blockade AUS$ 65,000 but markedly less cost-effective than Aldactone or spironolactone (potassium-sparing diuretic) at only AUS$ 5,000 per annum. Home exercise training (AUS$ 12,000) is even more cost effective than Beta-Blockade but not Aldactone.

Several studies have reported that the major issues in implementing exercise training in CHF patients are lack of referral and poor exercise adherence which are related to medical, demographics, psychological

and various social backgrounds. These factors include age, sex, race, physician recommendation, patients' beliefs about their illness, patient's expectation about cardiac rehabilitation, feelings of self-efficacy, mood and coping style (French, Cooper, & Weinman, 2006; Mampuya, 2012; Yohannes, Yalfani, Doherty, & Bundy, 2007).

There are inequalities in cardiac rehabilitation referral and exercise adherence that affect women, elders and minorities. A study by Yohannes. et al 2007 reported that woman showed poorer participation rates than men (Yohannes et al., 2007). The barriers to women's participation include the lack of financial, transportation difficulties and the lack of social and emotional support (Sanderson & Bittner, 2005). Older patients are less likely to be referred to participate in cardiac rehabilitation even though several studies have shown that the elderly have better outcomes (Ferrara et al., 2006; Hammill, Curtis, Schulman, & Whellan, 2010).

Several studies have also reported that ethnic minorities have limited participation in exercise training programs due to lack of accessibility to program sites, lack of insurance coverage and low patient referral rates (Balady et al., 2007; Gregory, Han, Morozova, & Kuhlemeier, 2006; Mazzini, Stevens, Whalen, Ozonoff, & Balady, 2008). Adherence is influenced by social, economic, health care teams and systems and other patient'-related factors (Conraads et al., 2012).

2.4 General therapy for heart failure

Chronic heart failure (CHF) can be treated by controlling the responsible pathophysiologic mechanisms such as improving the heart's ability to pump, reducing the workload and controlling sodium intake and water retention. The potential treatment of heart failure patients has increased recently with the advent of new drugs, surgery, including valve replacement, blood pressure (BP) and ischaemic control and wider use of several therapies such as exercise training, dietary advice and patient education. However, in spite of all this progress, improved prognosis in CHF patients is yet to be evidenced (Drechsler et al., 2005). It has been speculated that the lack of improvement could be due to poor implementation of current guidelines and exercise training prescription as well as modest patient compliance with drug and other therapies.

2.4.1 *Pharmacologic Treatment*

Initiating medication for CHF patients assists in the reduction of structural abnormalities and subsequent CHF symptoms. Pharmacological interventions for CHF include the use of diuretics, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), vasodilators, digitalis glycosides and beta-blockers. Based on guidelines for the diagnosis and treatment of chronic heart failure (Voors & van Veldhuisen, 2005), it is recommended that compensated CHF patients with or without left ventricular systolic dysfunction should be treated with triple drug

therapy namely diuretics, ACE-inhibitors and beta-blockers, unless contra-indicated or not tolerated.

Compelling evidence exists that blocking or limiting neurohormonal activation and the associated effects is important in retarding CHF progression and improving symptoms and survival in chronic CHF (Barlow et al., 1994; Braith & Edwards, 2003; Braith, Welsch, Feigenbaum, Kluess, & Pepine, 1999). ACE inhibitors, angiotensin receptor blockers (ARBs) and beta-blockers have been proven to provide cardiovascular benefits through the reduction of central circulatory congestion and/or oedema and also the improvement of systemic perfusion in CHF patients (Armstrong & Moe, 1993; Reyes, 2002). According to a study in the European Heart Journal (2012), two new drugs have been introduced namely Ivabradine and mineralocorticoid recepter antagonist eplerenone. Researchers believed that eplerenone's sole site of action is at the epithelial tissues, most notably the kidney, where it mediates transport of Na and K. It was soon recognized that aldosterone contributed to several diseases by causing oedema. They developed an antagonist of the mineralocorticoid receptor for the treatment of edematous states. Thus, spironolactone (Aldactone) was discovered. Spironolactone acts functionally as a competitive inhibitor of the mineralocorticoid (aldosterone) receptor, and although spironolactone is an effective mineralocorticoid receptor antagonist, it is not without limitations (J. J. McMurray et al., 2012).

2.4.1.1 Diuretics

Diuretics are important and remain the cornerstone of symptomatic treatment for CHF. Most diuretics act directly on the kidney by inhibiting solute and water reabsorption thus reducing excess body water. It has been suggested that the overall objective of diuretic therapy is to eliminate excess fluid from the lungs to an extent compatible with safe general haemodynamic responses (Reyes, 2002). Diuretics improve the symptoms of sodium and fluid retention, and increase exercise tolerance and cardiac function, regardless of New York Heart Association (NYHA) classification (Brater, 1998; McConaghy & Smith, 2004). Diuretic therapy also lowers blood pressure (BP) related to excess fluid in renal insufficient CHF patients. Furosemide is the most commonly used diuretic and its principal site of action is the thick ascending limb of Henle's loop, where it inhibits the reabsorption of sodium, potassium and chloride, thus decreasing water reabsorption.

2.4.1.2 ACE inhibitors

ACE inhibitors also improve symptoms, haemodynamics, and exercise performance in patients with CHF. A 31% reduction in mortality has been reported in CHF patients treated with the ACE inhibitor such as enalapril (CONSENSUS, 1987). It has been reported that ACE inhibitors increase serum sodium levels and are also associated with reduced heart size and thus reduced mortality in patients with systolic heart failure (Garg & Yusuf, 1995; Reyes, 2002). ACE inhibitors are also associated with reduced

hospitalization due to heart failure regardless of severity, although this benefit is more likely in patients with New York Heart Association (NYHA) classes III and IV (McConaghy & Smith, 2004). It modifies the remodeling process by influencing parameters such as LV end-diastolic and end-systolic volume and ejection fraction in both asymptomatic LV dysfunction post Myocardial Infarction (post-MI) and symptomatic patients with HF (Cohn, Ferrari, & Sharpe, 2000).

2.4.1.3 Beta-Blockade

Compensated CHF patients who are already taking ACE inhibitors and/or diuretics further reduce mortality if they also take a suitable beta-blocker; e.g. bisoprolol, metoprolol or carvedilol (Packer et al., 1993). Mortality may also be reduced with propranolol in patients who have an ejection fraction of less than 25% (Sturm et al., 2000).

Beta-blockade has effected on contractility, remodeling, autonomic tone, and arrhythmia burden. The study by Biykem Bozkurt et al. (2012) reported that there were no changes in systemic vascular resistance with carvedilol treatment; however, improvements in pulsatile arterial compliance and ventriculoarterial coupling suggested enhanced cardiac mechanoenergetic performance along with improved systemic arterial compliance (Bozkurt et al., 2012).

Beta-blockade consistently improved ejection fraction in both post-MI and HF patients irrespective of etiology. A small-scale study (n = 33) showed

that when metoprolol treatment was withdrawn after an average of 16 months' administration in patients with severe HF, LV function deteriorated in two-thirds of patients, and survivors benefited from re-administration of the drug (Cohn et al., 2000).

2.4.2 *Surgical Therapy*

Surgical CHF treatments are left ventricular muscle flaps, coronary artery bypass graft, reparative, reconstructive, excisional, ablative surgeries and cardiomyoplasty. The muscle flap (cardiomyoplasty) uses a pacemarker, which stimulates the flap to contract, thus contracting the left ventricle. Meanwhile, a reparative procedure improves cardiac haemodynamics and hence cardiac performance by correcting cardiac malfunction such as atrial and ventricular septal defect and mitral stenosis. Most CHF patients have myocardial ischaemia and infarction, therefore coronary artery bypass graft surgery improves cardiac muscle function through reconstructive treatment. Another way to improve the functional status of CHF patients is by cardiomyoplasty (Partial Left Ventriculectomy-Batistra) procedure which removes dilated and non-contracting myocardium and subsequent suturing the remaining viable myocardial tissue. However, the lack of a clear survival advantage and the relatively poor and inconsistent haemodynamic benefit of cardiomyoplasty have hindered its acceptance to date as an alternative treatment for patients with end-stage heart failure. The procedure was associated with high early and late failure rates due to only 26 percent event-free survival, and survival rates

of only 60 percent, during 3 years. The ultimate role of cardiomyoplasty in the treatment of heart failure will depend on the outcome of future developments to improve contractility and long-term durability (Voss & Lange, 2001).

Another popular intervention for CHF patients with LVEF below 30% is implantable cardio-version defibrillators (ICD) which resuscitate patients from sudden arrest. CHF patients with ICD's appear reluctant to participate in exercise training due to fear of exercise induced shock. A review of nine studies, comprising 1889 patients reported that seven shocks were reported in 834 patients with ICD's during exercise training, 166 shocks were recorded between exercise sessions and follow up (Isaksen, Morken, Munk, & Larsen, 2011). Some recommendations arose from this review; (1) patients with an ICD should be evaluated with an incremental exercise test before starting exercise training, and (2) exercise intensity should be considerably below the programmed ICD threshold to reduce the risk of shock. The HF-ACTION study documented that 45% of the 2331 patients included in the study had an ICD and only 1 patient had an ICD discharge, suggesting therefore that exercise is still safe and beneficial to CHF patients (O'Connor et al., 2009).

Angioplasty is another procedure to treat CHF patients caused by coronary artery disease and may be compounded by heart damage or a previous heart attack. Angioplasty is performed to treat narrowing or blockage of a coronary artery to the left ventricle. The procedure involves

placing a catheter with a small balloon on its tip into the narrowed artery and then the balloon is inflated and deflated. The procedure is sometimes followed by stenting, whereby by a stent is inserted into the artery to keep it open and restore normal blood flow.

Some CHF patients use a pacemaker implantation; a device that controls the heart rate. A pacemaker is an electrode attached to the tip of a wire, implanted inside the chest that sustains a regular rate when the heart is not beating normally.

2.4.3 *Exercise Therapy*

2.4.3.1 Chronological history of exercise therapy for heart failure patients

Based on CHF exercise training studies in the 1970s, acute myocardial infarction patients were immobilized for 4 to 8 weeks of bed rest to encourage the necrotic myocardium to form a scar. The reason for bed rest was due to concern that physical activity could lead to complications such as heart failure, cardiac rupture, dysrhythmias, re-infarction or aneurysm. Common opinion was that exercise training was not advisable in CHF patients at this time. We now know that prolonged immobilization did not speed up the healing process but exposed the patients to other complications such as muscle atrophy, decreased oxygen uptake, orthostatic hypotension, venous thrombosis and pulmonary embolism (Saltin et al., 1968).

In the late 1970s and early 1980s, several small studies (Froelicher, Battler, & McKirnan, 1980; Kallio, Hamalainen, Hakkila, & Luurila, 1979; Lee, Ice, Blessey, & Sanmarco, 1979; Saltin et al., 1968) were published on the effects of exercise training on cardiac function, mortality and re-infarction in cardiac patients. One study found that cumulative coronary mortality was lower in exercise training groups compared to controls (18.6% versus 29.4%) (Kallio et al., 1979). During the 1980s and 1990s, Connor et al. (Connor, Vlietstra, Schaff, Ilstrup, & Orszulak, 1988) found a 20% reduction of mortality from 4554 cardiac patients with exercise training. The study by Sullivan et al (1989) suggested that exercise training increases skeletal muscle vascular resistance and reduced leg blood flow to maintain arterial blood pressure and thus maintain perfusion of important non-exercising regions in chronic heart failure patient (Sullivan, Higginbotham, & Cobb, 1989). A review by May and colleagues (May et al., 2006) reported a reduction in mortality with exercise training; and, exercise training appeared safe for cardiac patients with coronary artery disease. During this century, two meta-analyses have reported improved peak oxygen uptake, quality of life and a decreasing trend of mortality rates in exercise training heart failure patients versus controls (M. F. Piepoli, Davos, Francis, & Coats, 2004; N. Smart & Marwick, 2004). In 2008, the largest randomized trial [HF-ACTION] to date with 2331 participants reinforced that exercise training in patients with systolic heart failure is safe. Perhaps disappointingly, the primary HF-ACTION finding was that exercise training

produced a non-significant reduction in the primary end points (all-cause mortality or all cause hospitalization), although these analyses were significant when adjusted for key variables such as beta-blocker use.

A number of studies (Braith & Edwards, 2003; Braith et al., 1999; Cider, Schaufelberger, Sunnerhagen, & Andersson, 2003; Oka et al., 2000) have demonstrated specific mechanisms of adaptation for exercise-induced benefit in CHF patients. Cardiac dysfunction in heart failure patients will decrease cardiac output, depress LVEF (which has an impact on both systolic and diastolic function), abnormal skeletal muscle metabolism (which will reduce mitochondrial enzyme activity) and muscle fibre type alterations. A study by Sarullo and colleagues (2006) suggested that peripheral factors may impair oxygen transport and utilization, and may reduce exercise performance in CHF patients (Maria Sarullo et al., 2006). Sarullo and colleagues (2006) suggested these impairments were due to apoptosis and chronic inflammation with associated skeletal muscle atrophy, a change in fibre type, bioenergetics affected by anaerobic metabolism and hence impaired skeletal muscle blood flow (Maria Sarullo et al., 2006). A Study by Esposito and colleagues 2010 stated that peripheral, rather than cardiac, factors might contribute to the limited exercise capacity in CHF. Biological changes to limited exercise capacity in CHF patients includes muscle atrophy, fiber type changes, reduced mitochondrial enzymes, decreased mitochondrial volume density and a vascular/skeletal muscle interface (with greater sympathetic

vasoconstrictor tone, decreased capillarity, and smaller capillary diameter). With the limited maximal cardiac output associated with CHF, the involvement of such a large muscle mass is thought to be a major factor limiting exercise capacity (Esposito, Mathieu-Costello, Shabetai, Wagner, & Richardson, 2010).

Thus, promoting exercise training does produce adaptive or physiological changes specific to mitochondrial activity at cellular and muscle fibre level in CHF patients.

2.4.3.2 Benefits of Exercise

a. Morbidity and mortality

Two systematic reviews have suggested exercise training reduces morbidity and mortality (M. F. Piepoli et al., 2004; N. Smart & Marwick, 2004). A trial by Belardinelli et al. (1999) reported that fewer cardiac-related deaths in the exercise training group (P=0.01); fewer hospitalization (P=0.02); and fewer cardiac events in the 12 months of exercise training in CHF patients compared to non-exercise group (Belardinelli, Georgiou, Cianci, & Purcaro, 1999). Piepoli's meta-analysis of randomized controlled trials showed overall reduction in mortality and a significant reduction in a composite of mortality and adverse events compared to sedentary controls. Interestingly, patients with LVEF< 27% showed a statistically significant mortality benefit whereas those with LVEF > 27% did not. Data also showed that CHF patients with lower classification NYHA (III and IV), elderly (> 60 years), lower peak VO_2 (< 15

ml/kg/min) and ischaemic cardiomyopathy are more likely to show a mortality benefit from exercise training (M. F. Piepoli et al., 2004). A review by Smart et al. (2004) indicated CHF patients with ischaemia may acquire lower functional capacity changes with exercise training compared to their non-ischaemic counterparts (N. Smart & Marwick, 2004). The relationship between mortality and functional capacity (Peak VO_2) is relevant because previous work has suggested peak VO_2 is the strongest predictor of mortality in CHF patients (Haass, Zugck, & Kubler, 2000; F. M. Sarullo et al., 2010).

In contrast with the meta-analyses mentioned previously, the HF-ACTION showed that exercise training resulted in a non-significant reduction in the primary end point of all-cause mortality or hospitalization (HR, 0.93 [95% CI, 0.84-1.02]; P=0.13). However, after adjusting for covariates and heart failure etiology from the study such as duration of the cardiopulmonary exercise test, LVEF, Beck Depression Inventory score and history of atrial fibrillation, exercise training was found to reduce the incidence of all-cause mortality or all-cause hospitalization by 11% (HR, 0.89 [95% CI, 0.81-0.991]; P=.03). The failure of the HF-ACTION trial to show mortality benefit may be explained by three factors. Firstly, adherence to exercise was below the study target, and this may have led to the intervention group producing much smaller (4%) improvements in peak VO_2, than those traditionally expected [15-17%]. Secondly, the results of HF-ACTION may have been affected by crossover to the exercise intervention in up to one

third of the sedentary controls. Finally, at the time HF-ACTION was designed moderate intensity continuous exercise was considered the gold standard in exercise programming and recent work has suggested high intensity and/or interval exercise may provide superior health benefits (N. A. Smart, Dieberg, & Giallauria, 2013; Wisloff et al., 2007).

A randomized study by McKelvie et al. (2002) (McKelvie et al., 2002) showed that there was no significant mortality or morbidity difference between outpatient – and home-based exercise training groups. A study by Belardinelli et al. (1999) reported that the rates of morbidity and mortality were reduced significantly in patients completing exercise training initially outpatient and later at home when compared to a sedentary control group (Belardinelli et al., 1999). Exercise adherence may influence the effect of mortality in CHF patients; a review by Tabet et al. (2009) stated that mortality benefits from exercise training are not related to exercise prescription but related directly to compliance of exercise training (Tabet et al., 2009). However, heart failure patients in exercise training and mortality studies perhaps do not represent real world patients. The real CHF patients are in general older, more likely to be female, and with several co morbidities such as diabetes and hypertension. In order to extrapolate data to the general population future exercise training studies as well as mortality studies need to include cohorts that are more representative of CHF patients in the wider community. Otherwise,

knowledge gained can only be translated to a minority (Niederseer, Thaler, Niederseer, & Niebauer, 2013).

b. Quality of Life

A large number of CHF patients still have poor quality of life regardless of recent improvements in pharmacological treatments (M. F. Piepoli et al., 2011). A study by Skotzko et al. (2000) showed that more than 50% of CHF patients were depressed (Skotzko et al., 2000). Exercise training has now become a cornerstone for implementing more efficient therapeutic approaches to improve quality of life. A systematic review by Williams et al. (2001) reported data from 16 studies, over two-thirds reported improved quality of life in CHF patients who exercised (Williams, 2001). A meta-analysis by Van Tol et al. (2006) also reported there was improved health-related quality of life in exercising CHF patients which was assessed through Minnesota Living with Heart Failure Questionnaire (MLWHFQ) (Van Tol, Huijsmans, Kroon, Schothorst, & Kwakkel, 2006). Exercise training in patients with chronic heart failure is useful for improving their psychosocial status. Improvements in psychological status seem to be independent of the aerobic gains (Koukouvou et al., 2004). Nevertheless, the efficacy of exercise training on functional capacity and quality of life is not yet known in terms of long-term effects, although it has been known to give benefits in the short term. Large, long-term, pragmatic trials of exercise training in patients with HF are needed to determine the effectiveness of exercise training on morbidity, quality of life, and mortality (M. F. Piepoli, 2013).

c. Neurohormonal Changes

Patients with CHF have a poor prognosis perhaps because of their abnormalities in several organ systems (Braith & Edwards, 2003) and the body attempts to reverse the effect of reduced cardiac output. The greater activation of the renin-angiotensin system contributes to neurohormonal excitation in CHF, including arterial and cardiopulmonary baroreceptors, central and peripheral chemoreceptors, cardiac chemoreceptors, and central nervous system abnormalities (Braith & Edwards, 2003). Impaired arterial and cardiopulmonary baroreflex control has been reported in animals and humans with chronic CHF (Tyni-Lenne, Dencker, Gordon, Jansson, & Sylven, 2001), Thus, it reduces peripheral skeletal muscle mass and abnormal reflex physiology in chronic heart failure (M. F. Piepoli et al., 2006).

Previous studies in subjects with normal left ventricular function have demonstrated that regular endurance exercise reduces central sympathetic tone, increases parasympathetic activity, decrease plasma renin activity and improves baroreflex sensitivity (Braith & Edwards, 2003; Tyni-Lenne et al., 2001). CHF patients get beneficial effects from exercise training in terms of reduced norepinephrine levels at rest and during exercise which in turn decrease central sympathetic nerve outflow, enhances vagal control and improves heart rate variability with a return to more balanced sympathetic-vagal tone. Exercise training also allows a significant reduction in the local expression of pro-inflammatory cytokines

such as tumour necrosis factor-alpha, interleukin 1-beta and interleukin-6. Inducible nitric oxide synthase in the skeletal muscle also provides a beneficial effect on peripheral inflammatory markers reflecting monocytes/macrophage-endothelial cell interaction. These local anti-inflammatory effects of exercise may attenuate the catabolic wasting process associated with the CHF progression (Braith & Edwards, 2003; Tabet et al., 2009; Tyni-Lenne et al., 2001). Endurance exercise studies in CHF patients have demonstrated a reduction in both brain natriuretic peptides and N-terminal pro-hormone brain natriuretic peptides levels (Berent et al., 2009; Maria Sarullo et al., 2006; Taub, Gabbai-Saldate, & Maisel, 2010). Pro-inflammatory cytokines and brain natriuretic peptides have been identified as prognostic cardiac markers in various CHF settings (Tabet et al., 2009; Taub et al., 2010).

d. Catecholamines

Catecholamines are organic compound that contain pyrocatechol with an alkylamine side chain such as norepinephrine, epinephrine and dopamine. Stimulation of the sympathetic cardioaccelerator nerves release the catecholamines epinephrine and norepinephrine.

Plasma levels of norepinephrine are elevated in both symptomatic and asymptomatic CHF patients. Catecholamines cause chronotropic and inotropic effects in CHF patients. Excess systemic catecholamines increase ventricular load secondary to vasoconstriction and sympathetic activity in CHF which are directly related to disease severity and survival.

Previously, animal studies have shown that norepinephrine is elevated in myocyte hypertrophy by stimulation of both α1 and β-adrenergic receptors in adult rat myocytes (Braith & Edwards, 2003; Braith et al., 1999). Additionally, high levels of norepinephrine are toxic to cardiac myocytes, and the mechanism appears to be β-adrenergic-stimulated apoptosis. A study by Tyni-Lenne et al. (2001) reported that there was a 26% reduction in plasma norepinephrine levels at rest and by 25-50% at peak performance in the exercise group compared to the non-exercise group in CHF patients (Tyni-Lenne et al., 2001).

e. Cytokines

Cytokines are a group of protein molecules with relatively small molecular weights (~ 15-30 kDa) that act as catabolic factors involved in the pathogenesis of peripheral muscle wasting and cardiac cachexia (Anker et al., 1997; Gielen et al., 2005). Patho-physiologically cytokines are secreted by cells in response to a variety of different stimuli and exert their effects by binding to specific receptors on the cell surface (Niebauer, 2008). Raised serum cytokines concentrations in CHF patients may exert endocrine effects and reductions in local cytokines expression may attenuate skeletal muscle wasting in CHF (Adams et al., 1999).

Cytokines may affect muscle metabolism and strength by direct effects on the sarcoplasmic reticulum Ca^{++}, adenosine triphosphate and phospholamban (as observed in cardiomyocytes) (Adams et al., 1999) or by stimulation of other pathologic factors, such as inducible isoform of

nitric oxide synthase (iNOS), which is stimulated by IL-1-beta and TNF-alpha via activation of nuclear factor-kappa β (J. McMurray, McLay, Chopra, Bridges, & Belch, 1990). The inflammatory response is caused by cytokines which may alter skeletal muscle histology and have a negative impact on left ventricular remodelling and cardiac contractility (N. A. Smart & Steele, 2011). Inflammation comprises muscle atrophy, increases fibre type switching from oxidative type I to glycolytic type IIb fibres, decreases myosin heavy –chain type I fibres, and mitochondrial enzymes involved in the oxidation of fatty acids. Decreases in cytochrome c oxidase and mitochondrial volume density are also observed (Niebauer, 2008). Inflammatory cytokines expression is also associated with progression of atherosclerosis, oxidative stress, nitric/oxide impairment, vasoconstriction, endothelial cell apoptosis, and adverse vascular remodelling (N. A. Smart, Larsen, Le Maitre, & Ferraz, 2011).

TNF-α and interleukin-6 (IL-6) (Levinger, Bronks, Cody, Linton, & Davie, 2005) are the most relevant cytokines associated with CHF; both cytokines are secreted by several different cell types and have a variety of immune and inflammatory actions. Exercise training in CHF patients has been shown to reduce pro-inflammatory cytokines and neurohormonal expression and attenuate catabolic factors involved in the pathogenesis of CHF (N. A. Smart & Steele, 2011). Serum TNF-α is reduced in CHF patients with increased skeletal muscle cross-sectional area and peripheral muscle strength during ≥ 5 sessions per week of physical training (Deswal et al.,

2001). TNF-α levels have been reported to be elevated in CHF patients and are the strongest predictors of weight loss (Niebauer, Clark, Webb-Peploe, & Coats, 2005). Data review by Smart. et al. (2011) reported reductions in serum IL-6 concentration although other work has reported physical training attenuates serum levels of TNF-α but not IL-6 in CHF (N. A. Smart & Steele, 2011).

Exercise training also improves the inflammatory profile in CHF by reduction of soluble apoptosis signalling molecules (Adamopoulos et al., 2002), and attenuation of monocyte-endothelial cell adhesive interaction (Adamopoulos et al., 2001), although there is no apparent relationship between changes in peak VO_2 and alterations in cytokines levels across a heterogenic patient group (N. A. Smart & Steele, 2011). It is unclear which exercise regime is optimal for effecting change in serum cytokines. Aerobic exercise programs may be more likely to produce changes in TNF-α compared with functional electrical stimulation or inspiratory muscle training (N. A. Smart & Steele, 2011).

f. Brain Natriuretic Peptides (BNP)

BNP is a 32 amino acid long molecule and is a product of cleavage of the prohormone BNP of which the other product is NT-proBNP. BNP is secreted and synthesized by cardiomyocyte stretch. BNP counteracts the detrimental effects of the sympathetic nervous system. BNP's haemodynamic effects arise from dilating arteries and veins as well as suppressing the renin-angiotensin-aldosterone system. Both BNP and NT-

ProBNP are released in response to volume or pressure overload from cardiomyocytes thus stimulating sodium and water excretion by the kidneys (Taub et al., 2010; Troughton & Richards, 2009).

Both BNP and NT-proBNP increase with age, sex, body mass index, renal function and severity of overall diastolic dysfunction, independent of left ventricular ejection fraction. BNP and NT-proBNP are lower in men than in women (Redfield et al., 2002; Taub et al., 2010; Troughton & Richards, 2009) and are elevated in CHF patients. BNP and NT-proBNP assays have been proposed as prognostic and diagnostic tools for mortality, repeated hospital admission, and myocardial infarction in patients with symptomatic CHF, and in patients with asymptomatic left ventricular dysfunction (Berent et al., 2009). A study by Tschope et al. (2005) stated that the independent predictor of severe diastolic dysfunction in subjects with normal LVEF is NT-proBNP > 600 pg/mL or BNP >100 pg/mL (Tschope et al., 2005). BNP >170 pg/mL in lean and 110 pg/mL in obese patients has 90% sensitivity for CHF (Tschope et al., 2005).

A systematic review by Smart et al. (2010) reported that exercise training reduced BNP levels (-79pg/mL [95% CI, -141 to 17]; P = .01) and NT-proBNP (-621 pg/mL [95% CI, -844 to -398] P < .00001) (N. A. Smart & Steele, 2010). Data collected also suggested that determination of the magnitude and rate of change in BNP and the N-terminal portion may be influenced by the weekly exercise energy expenditure and also exercise intensity. A

minimum weekly energy expenditure > 460 Kcal.week^{-1}) may be required to elicit changes in B-type natriuretic peptides.

g. ST-2

ST-2 is a member of the interleukin-1 receptor family and is produced by various cells, such as monocytes and macrophages. ST-2 with the transmembrane form (ST-2L) and secreted soluble form (sST-2) has a prognostic value in acute and chronic CHF patients. Soluble ST-2 (sST-2) is the truncated soluble receptor form that is secreted by cells into the circulation; it lacks transmembrane and intracellular domains. Meanwhile, ST-2L has three extracellular lgG domains, a transmembrane and intracellular domain (Bhardwaj & Januzzi, 2010). ST-2 has been found to be secreted when mechanical strain is applied to cardiomyocytes in response to injury and during ventricular remodelling (Bhardwaj & Januzzi, 2010; Taub et al., 2010). Interleukin 33 (IL-33), the functional ligand for ST-2, is also induced and released by cardiomyocytes. Cardiac remodelling has been associated with a greater rate of adverse outcomes among patients with heart failure (Urbano-Moral et al., 2012). Myocardial remodelling is a mechanism in the progression of CHF and a complex process involving cardiomyocyte hypertrophy, left ventricular dilation and fibroblast proliferation with collagen production (Bhardwaj & Januzzi, 2010). Soluble ST2 (sST2) is an interleukin-33 receptor. Soluble ST2 was found to be an independent prognostic factor in patients with myocardial infarction, sepsis and heart failure. Soluble ST2 appears to be a decoy

receptor that binds IL-33 and inhibits the membrane ST2 signalling pathway (Parenica et al., 2012). Several clinical studies have demonstrated sST-2 to be a biomarker of mechanical stress, myocardial fibrosis, atherosclerosis, autoimmunity and ventricular dysfunction in CHF. An elevated serum level of the soluble isoform of ST-2 is associated with poor prognosis and adverse outcomes in older patients with systolic and ischaemic CHF (Bayes-Genis et al., 2010; Broch et al., 2012; Shah, Chen-Tournoux, Picard, van Kimmenade, & Januzzi, 2010). ST-2 is a strong prognostic marker for short-term mortality risk and also an independent predictor of 1-year mortality in CHF patients (Daniels, Clopton, Iqbal, Tran, & Maisel, 2010; Eggers et al., 2010). ST-2 signalling plays a role in the balance of inflammation and neurohormonal activation (Bhardwaj & Januzzi, 2010). The effect of exercise training in producing changes in ST-2 in CHF patients is currently unknown. A review by Smart et al. (2010) reported that natriuretic peptides are significantly elevated in most CHF patients (N. A. Smart & Steele, 2010). In contrast, sST-2 is not elevated in every CHF patient because ST-2 responds more to injury and fibrosis; although the elevation is a sign of risk for complications (Bhardwaj & Januzzi, 2010). Natriuretic peptides may therefore be considered superior to sST-2 for establishing prognosis in the presence of disease, whereas sST-2 seem superior for establishing prognosis in CHF which contributes to risk stratification in an additive fashion and reflects specifically on cardiac remodelling. Soluble ST-2 (sST-2) is less affected by age, BMI, renal function

and prior history of CHF than BNP (Bayes-Genis et al., 2010; Daniels et al., 2010; Taub et al., 2010), although a combination of both biomarkers might be viewed as the best approach to determine prognosis in CHF patients.

2.4.3.3 Factors affecting responses to Exercise Training in clinical CHF

a. Age

The prevalence of Chronic Heart Failure increases linearly with increasing age (Kannel & Belanger, 1991). Despite the fact that 10% of CHF patients are over 80 years, most participating in clinical CHF studies are tend to below 65 and twice as likely to be male (J. McMurray, 2000). A study by American Heart Association (AHA)(2003) has reported that age is one of the factors that affects exercise adherence of CHF patients (Pina et al., 2003). Although exercise training is beneficial in older aged CHF, several studies did not support this finding (Brubaker, Moore, Stewart, Wesley, & Kitzman, 2009; Sumukadas, Witham, Struthers, & McMurdo, 2007; Witham, Argo, Johnston, Struthers, & McMurdo, 2007). In addition, beneficial changes seem smaller in patients older than 70 years (Gianuzzi et al., 2001; M. Piepoli, 1998), as age determines physical fitness. Previous studies have investigated the effect of age in exercise training and found that exercise training is safe. Exercise training is also beneficial for even older age (average age of 81 years) CHF patients (Owen & Croucher, 2000; Willenheimer, Erhardt, Cline, Rydberg, & Israelsson, 1998). There are several potential pathophysiological benefits of exercise training for older age patients with chronic heart failure. Exercise training improves endothelial

function and blood flow to skeletal muscle (Hornig, Maier, & Drexler, 1996; Witham, Struthers, & McMurdo, 2003). The effects of strength conditioning on skeletal muscle function and mass were determined in older men. Resistance training improved peak VO_2, Vastus Laterlis capillarity, and citrate synthase in a 12-wk strength training program of 8 repetitions per set; 3 sets per day and 3 days per week at 80% of one repetition maximum (1 RM). Strength gains in older men were associated with significant muscle hypertrophy with an increase in myofibrillar protein turnover (Frontera, Meredith, O'Reilly, Knuttgen, & Evans, 1988). Exercise training improves autonomic activity by reducing sympathetic activation and norepinephrine level. It also improves heart rate variability (Keteyian et al., 1999; Kiilavuori, Naveri, Leinonen, & Harkonen, 1999; Witham et al., 2003) by affecting circulating factors and reducing resting levels of angiotensin-II, aldosterone, vasopressin, neuropeptides Y, and atrial natriuretic peptides (Braith et al., 1999; A. Gordon et al., 1997).

Aerobic exercise training in older adults reduces the minute ventilation and improves respiratory function, vasoconstrictive effects of the ergoreceptor reflex and QT dispersion on the electrocardiogram, a marker for malignant ventricular arrhythmias in CHF (Ali et al., 1999). Exercise training improves exercise capacity, coordination, balance and muscle strength for all older CHF patients (Kavanagh et al., 1996; Sturm et al., 1999)

Exercise training also reduce resting pulse rate and pulse rate at a fixed submaximal workload (Sullivan, Higginbotham, & Cobb, 1988). Afterload is reduced and blood vessel compliance improves leading to a low rate of double pressure product during certain workload (Belardinelli et al., 1999; Coats et al., 1992).

b. New York Heart Association (NYHA)

New York Heart Association (NYHA) is the most commonly used classification system for heart failure severity. It places patients in one of four categories based on their limitation during physical activity (Rossi, 1967). CHF patients in NYHA classes III-IV have low peak VO_2 probably due to lack of physical activity and abnormalities within the skeletal muscles. Meanwhile, stage II have slight limitation and stage I has no limitation in physical activity (Rossi, 1967). Caution is warranted when using NYHA class to discuss exercise limits, as patients can move in and out of these stages rather quickly such as high salt in food and subsequent volume retention when "wet", or conversely over diuresis when "dry". An alternative has been described by Weber and Janicki using class from A to D. The four classes were defined: as functional class A, > 20 ml/kg/min, class B, 16-20 ml/kg/min, class C, 10-15 ml/kg/min and class D, < 10 ml/kg/min. They have used the designation of A to D in place of NYHA clinical classification of I to IV to avoid confusion. Indeed, they highlighted the mechanisms of exercise intolerance using

non-invasive haemodynamic measures(Weber, Kinasewitz, Janicki, & Fishman, 1982).

At present, the relationship between NYHA and specific components of fitness such as quickness, agility, balance or muscular endurance has not been established. This work focuses on the four categories of NYHA classes in heart failure patients. NYHA class III and IV patients which are the most severe groups seem to gain more benefit from exercise training as there is a reduction in total cardiac mortality and hospitalization (Holloway et al., 2012; M. F. Piepoli et al., 2004). Holloway et al. (2012) reported that LVEF increased from 39% pre-exercise training to 44% after 8 weeks of exercise training in NYHA III and IV ($p<0.01$) (Holloway et al., 2012). Meta-analysis by Haykowsky and others (2007) has reported improvements in LVEF, end-diastolic volume (EDV) and end-systolic volume (ESV) in CHF patients in response to exercise training (M. J. Haykowsky et al., 2007). The study by Haykowsky et al. (2013) recently reported no significant change in LVEF when comparing high versus moderate intensity interval training (M. J. Haykowsky et al., 2013).

c. Cardiac Systolic Function [Left Ventricular Ejection Fraction (LVEF)]

Left ventricular ejection fraction (LVEF) has been used as a measurement for cardiac function during exercise training in CHF patients. It determines how much blood is pumped from the left and right ventricle with each heart beat. The normal range is between 55-70%. Tissue Doppler (TDI) imaging is a complementary ultrasound technique that has also been

used to allow direct quantification of myocardial diastolic and systolic behaviour.

A meta-analysis by Haykowsky et al. (2007) reported that there was a significant improvement in LVEF through exercise training. The weighted mean difference (WMD) for LVEF was significantly improved for aerobic exercise training which involved 9 trials and 538 patients; There was no significant improvement in LVEF, end-diastolic volume (EDV) or end-systolic volume (ESV) with isolated strength training or with combined aerobic and strength training (M. J. Haykowsky et al., 2007). Exercise training enhanced preload, vascular reserve and myocardial contractility thus increased the ejection fraction and reversed remodelling in stable individuals with HF. Aerobic training reversed Left Ventricular (LV) remodelling in CHF patients (M. J. Haykowsky et al., 2007). Although exercise training improved LVEF, the study by Cohen-Sohal et al. (1999) of 150 CHF patients showed that the measured functional capacity of CHF patients was unrelated to resting LVEF, probably because LVEF is dependent on cardiac pre-load whereas functional capacity is not (Cohen-Solal, Logeart, Guiti, Dahan, & Gourgon, 1999). High intensity (95% peak heart rate) interval exercise may produce the greatest improvements in systolic function (N. Smart, 2011). A recent study showed that high intensity exercise training increased LVEF by 10 percentage points (Wisloff et al., 2007). However, at the conference of the European Society of Cardiology (ESC) 2014, preliminary findings on high intensity

interval training in CHF provided less enthusiastic results. The final data have not yet been published (Muramatsu & Ozaki, 2014).

Exercise training generates antioxidative effects through reduction of vascular expression of NADPH oxidase and AT1 which decrease the generation of reactive oxygen species, thus improved acetylcoline-mediated coronary vasodilatation and decreased Angiotensin-II, induced vasoconstriction is observed. NADPH oxidase (nicotinamide adenine dinucleotide phosphate-oxidase) is a membrane-bound enzyme complex and AT1 is a class of G-protein-coupled receptors with Angiotensin-II as their ligands. This contributes to the reduction of peripheral resistance with improved left ventricular ejection fraction from restoration of endothelial function (M. F. Piepoli, 2013).

d. Cardiovascular Fitness

Peak VO_2 is the gold standard measure of cardiovascular fitness and predicts mortality in chronic heart failure patients (Ismail, McFarlane, Dieberg, & Smart, 2014; K. Meyer et al., 1996). Other related metabolic measures of cardiovascular fitness, such as V_E/VCO_2, can provide additional prognostic information. V_E/VCO_2 is the slope of relationship between ventilation and CO_2 production, or ventilatory efficiency, and can predict outcomes for CHF patients. Although the V_E/VCO_2 slope is reproducible and provides important prognostic information for CHF patients, several studies have addressed the ability of V_E/VCO_2 slope to detect training effects with conflicting results (Belardinelli, 2007; Belardinelli

et al., 2006). Moreover, a recent review showed that intermittent exercise elicits superior improvements in V_E/VCO_2 slope compared to continuous exercise training (N. A. Smart, Dieberg, et al., 2013).

Another popular method in cardiovascular fitness measurements for CHF patients is the Ventilatory Anaerobic Threshold (Vt). Vt is a reproducible non-invasive index of the rise in blood lactate during exercise in CHF patients. Sullivan et al. (1990) reported that there were changes in the ventilatory anaerobic threshold after exercise training that reflect changes in accumulation of blood lactate and hence changes in the exercise tolerance of CHF patients (Sullivan & Cobb, 1990; Sullivan et al., 1989). Exercise training delays the blood lactate accumulation and decreases VCO_2 ventilation and the respiratory exchange ratio (RER) and thus increases sub-maximal and maximal exercise performance (Arena, Myers, Aslam, Varughese, & Peberdy, 2004; Corra et al., 2012).

A meta-analysis found objective measures of physical capacity such as peak VO_2, improved anaerobic threshold and reduced V_E/VCO_2 (Forissier, Vernochet, Bertrand, Charbonnier, & Monpere, 2001; Fraga et al., 2007; Levinger et al., 2005; Nishi et al., 2011). A previous review by Smart et al. (2004) found that there was an increment of 16.8% ± 8.0% mean maximal oxygen uptake in 57 studies. The greatest mean increase in peak oxygen consumption came from 40 studies that involved continuous or intermittent aerobic exercise which was 16.5% ± 6.9% (95% CI, 14.3% to 18.7%). The same review also stated that aerobic and combined aerobic

and strength exercise training increases peak VO_2 by 16.5 and 15%, respectively, versus 9% in three studies that used strength training alone. It seems that any form of exercise training is beneficial to CHF patients, although effects size varies with exercise modality. Result showed a similar magnitude of change in functional capacity with both intermittent and continuous exercise training (N. Smart & Marwick, 2004).

Exercise training improved peak VO_2 for both ischaemic and non-ischaemic CHF patients (Keteyian et al., 1996). The prognosis of patients with ischaemic heart failure was worse than in patients with a non-ischaemic aetiology. The term 'non-ischaemic heart failure' includes various subgroups such as hypertensive heart disease, myocarditis, alcoholic cardiomyopathy and cardiac dysfunction due to rapid atrial fibrillation. Some of these causes are reversible. The therapeutic effect of essential drugs such as ACE inhibitors, beta-blockers and diuretics does not, in general, significantly differ between ischaemic and non-ischaemic heart failure. However, in some trials, response to certain drugs (digoxin, tumor necrosis factor-alpha, inhibition with pentoxifylline, growth hormone and amiodarone) was found to be better in non-ischaemic patients. Patients with ischaemic heart failure and non-contracting ischaemic viable myocardium may, on the other hand, considerably improve following revascularization. Hence, the aetiology of heart failure should be determined routinely in all patients (Follath, 2001).

Exercise increased mitochondrial density by restoring calcium cycling and improved oxidative capacity of trained skeletal muscle (N. Smart, Haluska, Jeffriess, & Marwick, 2007). It regulated the activity of Ca^{2+}-regulating proteins, such as sarcoplasmic reticulum Ca^{2+}-ATPase, phospholamban, the ryanodine receptor and the Na^{+} and Ca^{2+} exchanger, which increased myofilament Ca^{2+} sensitivity and, thus, myocyte contractility (M. F. Piepoli, 2013).

According to a recent study by Haykowsky et al, HFpEF patients have a normal preload reserve which normally occurs at a much higher LV filling pressure, suggesting non-cardiac peripheral factors contribute to reduced peak VO_2 (peak exercise oxygen uptake) and to its improvement after endurance exercise training (M. J. Haykowsky & Kitzman, 2014).

Two studies have examined the chronic effects of exercise training on rest and exercise CV function in HFpEF. In these studies there were no changes in peak exercise stroke volume, cardiac output, or brachial arterial endothelial function in response to cuff ischaemia. Accordingly, the improvements in peak VO_2 were likely due to enhanced diffusive oxygen conductance or greater oxygen extraction by the active muscles (M. Haykowsky, Brubaker, & Kitzman, 2012; M. J. Haykowsky & Kitzman, 2014; Kitzman et al., 2013)

Maximal aerobic capacity is a strong prognostic factor in patients with HF and determines the amount of activities of daily life CHF patients can

perform independently (Corra et al., 2012). Although exercise training improved exercise capacity, level of daily activity may not increase after exercise training (Gottlieb et al., 1999; Willenheimer et al., 1998). CHF patients undertake less activity compared to healthy individuals (Oka, Stotts, Dae, Haskell, & Gortner, 1993) and it is not clear why this should be. CHF patients need a higher percentage of their peak VO_2 compared to healthy persons to perform daily life activities (Kervio, Ville, Leclercq, Daubert, & Carre, 2004). According to K Meyer (2001), pathology and exercise tolerance of patients with CHF allow only a few selected activities to be performed, such as walking and cycle ergometer training. There is no consensus at present as to an optimal parameter for measuring intensity. An intensity of 40-80% peak oxygen consumption (VO_2) has been applied successfully. A heart rate reserve of 60-80% or 75% of peak heart rate was used as a guide to exercise intensity without consideration of the impaired force-frequency relationship in myocardial performance. Because intensity, duration, and frequency of exercise are closely interrelated, initial exercise should be kept at 40-50% peak VO_2 with exercise duration of > 3-5 min per session performed several times daily. Resistance training can be recommended when small muscle groups are involved, using short bouts of work phases and small numbers of repetitions. To increase respiratory muscle strength and endurance, resistive inspiratory muscle training at intensity 25--35% of maximum

inspiratory pressure and performed 20-30 min per day, is recommended(K. Meyer, 2001).

Peak VO_2 will increase using low or moderate intensity exercise training but a few small studies (Dubach et al., 1997; Freyssin et al., 2012; Nilsson, Hellesnes, Westheim, & Risberg, 2008; Patwala et al., 2009) have suggested that high intensity interval exercise may provide larger improvements in peak VO_2. A recent study by Wisloff demonstrated a 46% improvement in peak VO_2 for high-intensity exercise training compared to only 14% of moderate-intensity exercise training (Wisloff et al., 2007).

2.4.3.4 Safety of exercise training

According to a systematic review by Smart et al. (2004) (N. Smart & Marwick, 2004), which included 81 studies of which 30 were randomized controlled trials, there were no reports of deaths directly related to exercise during more than 80,000 patient-hours of exercise training. Properly supervised exercise testing and training is therefore safe, even in high risk populations such as heart failure patients.

The American College of Sports Medicine (ACSM) and American Heart Association (AHA) have recommended that CHF patients need to be screened prior to exercise training, including exercise stress testing, in an attempt to circumvent any complications (Hunt et al., 2001; Mazzeo et al., 1998). Absolute and relative contraindications to exercise training are considered for CHF patients. Medical or health practitioners should perform and carefully review the pre-exercise test evaluation and prior

medical history. These help ascertain contraindications and the safety of the exercise testing and training. It is advisable that CHF patients with absolute contraindication not perform exercise testing or training until such conditions are stabilized or adequately treated. Patients with relative contraindications may be allowed to perform testing and exercise training, only after evaluation of the risk/benefit ratio. ACSM has listed guideline criteria for absolute contraindications to exercise testing (Mazzeo et al., 1998). Beside the aforementioned guidelines, a review by Meyer et al. (2001) has suggested specific relative contraindications for exercise training in CHF patients. These criteria involved patients who had an increase of ≥ 1 kg body weight within 24 hour; decreased in systolic blood pressure during exercise; concurrent continuous or intermittent dobutamine therapy; New York Heart Failure functional class IV; complex ventricular arrhythmia at rest or appearing during exertion and/or at a resting heart rate ≥ 100/min (K. Meyer, 2001).

2.4.3.5 Exercise Prescription

The optimal exercise program design is still perhaps undefined in CHF patients. Aerobic training leads to increase haemodynamic changes (Belardinelli, Georgiou, Scocco, Barstow, & Purcaro, 1995; Maiorana et al., 2011), altered vascular function (Tabet et al., 2009), and decreased heart rate and stroke volume at rest and increased chronotropic reserve and heart rate recovery during exercise (Tabet et al., 2009). Due to pathology and exercise intolerance of patients with CHF, most researchers use cycle

ergometer training for aerobic training because it allows exercising at very low work load and ease of monitoring of heart rate, rhythm and blood pressure. Cycle ergometry appears to be ideal for applying interval training (K. Meyer, 2001). However, in HF Action more subjects used treadmills rather than bikes for training. Normally CHF patients complete continuous or interval aerobic exercise with additional resistance training. HF patients are often hindered by skeletal muscle weakness, particularly at the level of the upper limb. A review by Smart et al. (2013) stated that the combination of intermittent and strength exercise training increased peak VO_2 to a greater extent than intermittent exercise training alone (N. A. Smart, Dieberg, et al., 2013). According to this review, the mean difference in peak VO_2 between combined strength training and intermittent exercise training versus intermittent exercise was 1.14 ml kg^{-1} and the difference between intermittent exercise and continuous exercise training groups was 0.65 ml kg min^{-1}. There was a reduction in V_E/VCO_2 slope of 1.42 with intermittent compared to continuous exercise training. The mean differences are not only statistically significant but also have clinical significance in CHF patients (N. A. Smart, Dieberg, et al., 2013).

Resistance training has anti-inflammatory effects which improve insulin resistance and strength in CHF patients (Nishiyama et al., 2006). A study by Winkelmann et al. (2009) showed that inspiratory aerobic muscle training (IMT) with a respiratory muscle-specific training device increased

cardiorespiratory responses compared to a control group without IMT in heart failure patients. (Winkelmann et al., 2009).

Several studies have demonstrated the benefits of short term exercise training, of less than 12 weeks, in HF patients (Belardinelli et al., 1999; Sturm et al., 1999; Wisloff et al., 2007). However, some randomized control trials also showed that patients with CHF have benefited from long term, more than 12 weeks exercise training (Braith et al., 1999; Dracup et al., 2007; Klecha et al., 2007). It has been observed that the functional capacity improvements from exercise training are positively influenced by the duration of the program, frequency, kilocalories expended and session duration (Ismail et al., 2014; K. Meyer, 2001).

Current guidelines recommend dynamic resistance training to be included as an adjunct, and not as a substitute for aerobic training. Using a combination of aerobic and dynamic resistance training in individuals with HF has been shown to positively impact muscular strength and endurance, in addition to exercise capacity, symptoms (fatigue and dyspnoea), 6-minute walk distance, and quality of life (Hare et al., 1999; Pozehl, Duncan, Hertzog, & Norman, 2010).

According to an Exercise and Sport Science Australia (ESSA) Position Statement on exercise training and chronic heart failure, CHF patients from all NYHA classifications are recommended to do exercise training with the frequency between 4-7 days a week and exercise intensity below myocardial ischaemic threshold. The duration of exercise should start at

10 to 15 minutes, at the target exercise intensity, and gradually increase to 45-60 minutes based on patient's progress and tolerance (Selig et al., 2010). Whilst this exercise prescription cannot be considered inappropriate, a small volume of recent work has shown high intensity interval exercise training may be superior for eliciting improvements in peak VO_2 and systolic heart function (Wisloff et al., 2007). Moreover, moderate intensity exercise training has yet to demonstrate a clear mortality benefit. Published trials of high intensity interval exercise training have produced large effect sizes in terms of improvements in peak VO_2 and cardiac function (Wisloff et al., 2007) . The underlying success of Wisloff's work in 2007 was that interval exercise allows for rest periods that make it possible for patients with heart failure to perform the total work of exercise at high intensity; exercise at high intensity is the major determinant of adaptation. Moreover, in Wisloff's work the comparison (continuous exercise) group completed exactly the same amount of work, thus removing ambiguity over dose-responses. Based on the study, published by Norton et al. (2010), there are five categories of exercise intensity involved when physiological stress is placed on the exercising individual (Norton, Norton, & Sadgrove, 2010). The categories are 'sedentary', 'light', 'moderate', 'vigorous' and 'high intensity' according to intensity based on HRmax, range of METs level, VO_{2max} and heart rate reserves cut-offs. The classification system also includes subjective measures such as Rate Perceived Exertion (RPE).

2.5 Assessing heath care interventions

Prior to 1970's a sedentary lifestyle, consisting of no physical activity was recommended to chronic heart failure patients. Late 1970's and early 1980's several small studies found exercise training to improve physical fitness and quality of life and re-infarction rates in cardiac patients (Froelicher et al., 1980; Saltin et al., 1968). Between the 1980's and late 1990's, the first randomized control trial (RCT's) suggested possible mortality and morbidity benefits for CHF patients (O'Connor et al., 2009). Subsequently, in 2000's meta-analyses confirmed the likelihood of a mortality benefit, improved cardiac function and Quality of Life (QoL) (M. J. Haykowsky et al., 2007; M. F. Piepoli et al., 2004; N. Smart & Marwick, 2004). In 2008 HF-ACTION (O'Connor et al., 2009) (the largest RCT to date - 2331 patients) reinforced that exercise training is safe and improved fitness, but mortality improvements remain unclear.

Systematic Review and Meta – Analysis

To access health care interventions, this study used systematic reviews and meta-analysis of exercise training studies in heart failure patients. This practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research (Sackett, Rosenberg, Gray, Haynes, & Richardson, 1996).

The evidence was assessed based upon three criteria; first, the strength of evidence which is categorised as is the level and quality. Second, size of

effect or the distance of the null value of the measure of treatment effect and values included in the confidence interval (95%CI); it is the summary measure of effect based upon the studies included in the systematic review. Third, the relevance of the evidence which relates to efficacy in a clinical setting, based mainly upon the outcome measures used. Included studies were randomized controlled design or controlled parallel trials of exercise training in chronic heart failure patients. The data collected for the meta-analysis can be either aggregate or individual patient data. These methods are an important for assessing health care interventions. They complement and synthesize data from prospective randomized controlled trials, which can often be conflicting.

2.5.1 *Systematic Review*

All relevant data and randomized control trials related to chronic heart failure and exercise training were included to minimise systematic biases and chance effect. Then, the evidence was appraised and synthesised from these scientific studies.

2.5.2 *Meta-analysis*

Results from all eligible randomized control trials relating to exercise training in chronic heart failure were pooled so a meta-analysis could be conducted. Basically, meta-analysis is a statistical technique for combining the relevant data from single trials. The data to be included in a meta-analysis is extracted from published studies or obtained directly from the authors. Meta-analysis is the hallmark of evidence based

practice and has been used to assess the clinical effectiveness interventions of exercise training in chronic heart failure patients because it provides a precise estimate of treatment effect.

2.5.3 *Assessment of evidence*

The strength of evidence is based on levels of evidence, study quality, statistical precision and effect size.

a. Level of evidence

Level of evidence was used to assess the clinical questions for interventions, diagnosis, prognosis, aetiology and screening. Difference research designs were included to address these clinical questions by classifying the level of evidence. Based on the designation level of evidences from Australian National Health and Medical Research Council (NHMRC); level 1 evidence is likely most reliable evidence which minimized bias in representing research results. Level I evidence is evidence obtained from a systematic review of all relevant randomized controlled trials (Merlin, Weston, & Tooher, 2009). Level II evidence is likely high reliable from properly-designed randomized controlled trial of exercise training in chronic heart failure. The data from level II was pooled to create level I evidence which can minimized bias.

b. Study quality

PEDro scale was used as a method to measure quality of study within a study design. PEDro scale is an 11- item scale designed to develop rate quality of RCT on PEDro , the physiotherapy evidence database.

c. Statistical precision and effect size

P-value of <0.05 was used for measuring of precisions to estimate the treatment effect, indicated by the 95% confidence interval. These values reflect the degree of certainty about the existence of a true effect in these works.

2.6 Summary of chapter and Conclusions

These methods of combining, reviewing and analysing data are important for assessing health care interventions. They are complement to and not a replacement for prospective randomized controlled trials. We used explicit methods and conducted the review on the trials reliably. We aim to minimize biases and chance effects and accurately assess study quality of published studies. We gathered and identified all relevant trials that related to chronic heart failure and exercise training. Finally, these help us to obtained statistically accurate result for this thesis. As conclusion exercise training seems to be safe and information from this chapter will assist health practitioners and exercise specialists in designing exercise prescription and assessing health care interventions based on the current scientific evidences in HF patients.